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Technetium-99m Methoxyisobutyl Isonitrile Scintigraphy of Bone Metastasis in Three Patients with Differentiated Thyroid Cancer

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ABSTRACT. We studied the usefulness of ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) scintigraphy in the detection of bone metastases and in evaluation of therapeutical response to ^{131}I-Na in three patients with differentiated thyroid cancer.

On ^{99m}Tc-MIBI scintigraphy, increased accumulations were observed in all bone metastatic lesions (14 lesions), whereas on bone scintigraphy using ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) both increased (eight lesions, 57%) and decreased (six lesions, 43%) accumulations were observed. Within two months after ^{131}I-Na treatment, all 14 lesions were unchanged on bone scintigraphy. However, on ^{99m}Tc-MIBI scintigraphy, disappearance of uptake (six lesions, 43%) and decreased uptake (seven lesions, 50%) were observed in 13/14 lesions (93%).

Therefore, ^{99m}Tc-MIBI scintigraphy was useful not only in the detection of bone metastatic lesions but also in evaluation of the therapeutical response to ^{131}I-Na in differentiated thyroid cancer.

Key words : ^{99m}Tc-MIBI Scintigraphy — Bone Metastasis — ^{131}I-Na treatment — Differentiated Thyroid Cancer — Bone Scintigraphy

In the lesions of bone metastasis from differentiated thyroid cancer, in which exclusive osteolysis associated with little bone formation occurs, either decreased or slightly increased uptake of ^{99m}Tc labelled phosphorus compound on bone scintigraphy is frequently observed.[1] Consequently both bone and tumor scintigraphies are frequently used to detect bone metastasis from differentiated thyroid cancer.

In recent years, ^{99m}Tc-methoxyisobutyl isonitrile (^{99m}Tc-MIBI) has been developed as a myocardial perfusion imaging agent. It has been also reported that this radiopharmaceutical accumulates in malignant lesions of the breast, lung and thyroid gland.[2,3] In cases of distant metastasis and incomplete surgical extirpation of a lesion from differentiated thyroid cancer, ^{131}I-Na therapy has been employed. ^{131}I-Na therapy is effective for the

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improvement of QOL due to bone pain as well as for the reduction of the lesion size in some patients with bone metastasis.

Abnormal sites on bone scintigraphy are often recognized as increased or decreased lesions, reflecting increased or decreased bone formation. ^{99m}Tc-MIBI scintigraphy has a high detection rate, like ^{131}I-Na and ^{201}Tl scintigraphies, for the localization of metastasis in thyroid cancer.[7] In addition, this method can be used without discontinuation of thyroid hormone replacement for hypothyroidism after total thyroidectomy, and unlike with ^{131}I-Na scintigraphy it does not require an iodine-free diet.[7] ^{99m}Tc-MIBI scintigraphy is also more sensitive than ^{201}Tl scintigraphy for the detection of bone lesions.

We investigated whether ^{99m}Tc-MIBI scintigraphy is useful for the detection of bone metastases and evaluation of the therapeutic effect of ^{131}I-Na in three patients with differentiated thyroid cancer.

MATERIALS AND METHODS

The subjects were three patients, one man, and two women, aged 41, 51 and 64 years old, respectively, with multiple bone metastases from differentiated thyroid cancer ; one papillary, one follicular, and one mixed papillary and follicular adenocarcinoma, respectively. ^{99m}Tc-MIBI scintigraphy was performed within one week after bone scintigraphy using ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP). For ^{99m}Tc-MIBI scintigraphy, a tracer of 370 MBq was injected intravenously, and 15 min later both a whole-body image and spot images of the suspected lesions were obtained, using a gamma camera equipped with a high-resolution low-energy collimator.

In all three patients total thyroidectomy was performed as ablation of remnant of thyroid gland for ^{131}I-Na treatment.

Bone metastases were confirmed by diagnostic imaging with CT, MRI and radiography as well as by the clinical course. As a radioisotope treatment, ^{131}I-Na of 3.7 GBq was administered orally to each patient. Within two months after ^{131}I-Na treatment, ^{99m}Tc-MIBI scintigraphy was performed again.

Concentrations of serum thyroglobulin (Tg), which was used as a marker of thyroid cancer, were determined by an immunoradiometric assay (normal range ; <50 μg/L).

RESULTS

A summary of the scintigraphic findings made by ^{99m}Tc-HMDP and ^{99m}Tc-MIBI in three patients with bone metastasis from differentiated thyroid cancer is shown in Table 1. On bone scintigraphy using ^{99m}Tc-HMDP, both increased (eight lesions, 57%) and decreased accumulations (six lesions, 43%) were observed in all three patients ; for example, bone scintigraphy of Case No. 1 was shown in Fig 1.

The increased lesions were in the orbit, rib, thoracic and lumbar vertebrae, ischium and femur, while the decreased lesions were in the sternum, ilium, sacrum, and sacroiliac joint. On the other hand, on ^{99m}Tc-

TABLE 1. Findings of bone and ^{99m}Tc-MIBI scintigraphies in three patients with bone metastases from differentiated thyroid cancer

Case No	Metastatic Site(s)	^{99m}Tc-HMDP	^{99m}Tc-MIBI
1	Lt. orbit	increased	increased
	Sternum	decreased	increased
	Lt. 7th Rib	increased	increased
	Th12	increased	increased
	Lt. Ilium	decreased	increased
2	Rt. Pubic Bone	decreased	increased
	Rt. Ischium	increased	increased
	Sacrum	decreased	increased
	Rt. Femur	increased	increased
	L2	increased	increased
	Lt. Sacroiliac Joint	decreased	increased
3	L3	increased	increased
	L4	increased	increased
	Sacrum	decreased	increased

Fig 1. Bone scintigraphy (left : anterior view, right : posterior view) on admission in Case No. 1. Increased accumulations were observed in the upper rim of the orbit, lower thoracic vertebrae, upper lumbar vertebrae and left rib, while decreased accumulations were noted in the lower part of the sternum and left ilium.

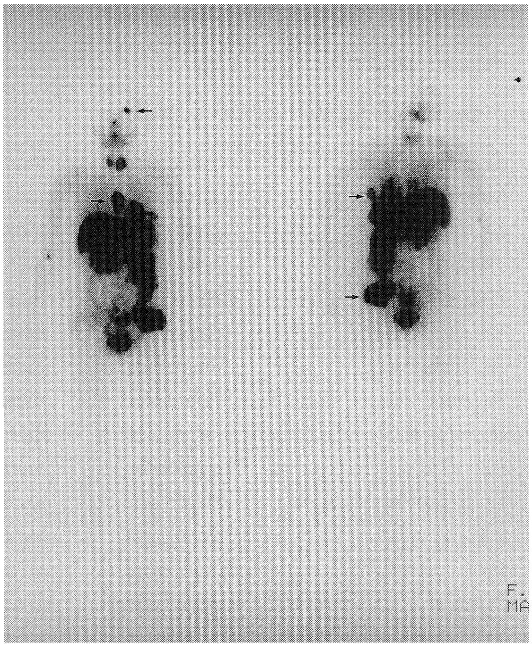

Fig 2. ^{99m}Tc-MIBI scintigraphy (left : anterior view, right : posterior view) on admission in Case No. 1. Both a primary tumor of the left thyroid lobe and bone metastases were imaged.

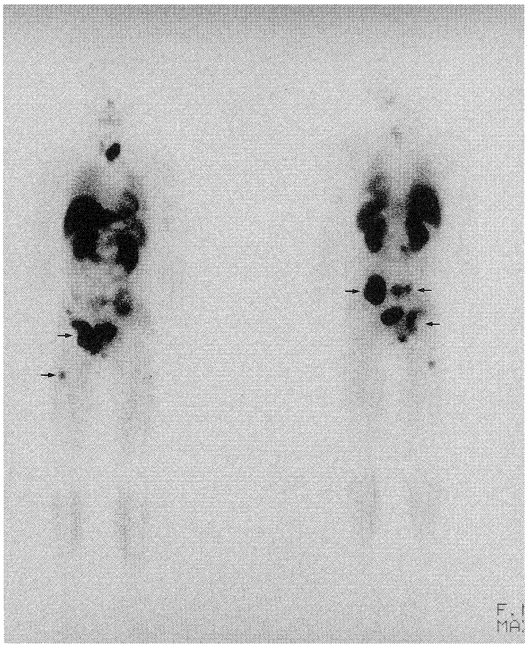

Fig 3. ^{99m}Tc-MIBI scintigraphy (left : anterior view, right : posterior view) on admission in Case No. 2. Increased accumulations in bone metastatic lesions were noted in the right pubic bone, sacrum, left sacroiliac joint, right ischium, lumbar vertebra and right femur.

Fig 4. ^{99m}Tc-MIBI scintigraphy (left : anterior view, right : posterior view) after ^{131}I-Na treatment in Case No. 1. Increased accumulations of bone metastatic lesions in the thoracic vertebrae, and left ilium as well as the thyroid gland disappeared, and those in the left rib, left orbit and sternum decreased.

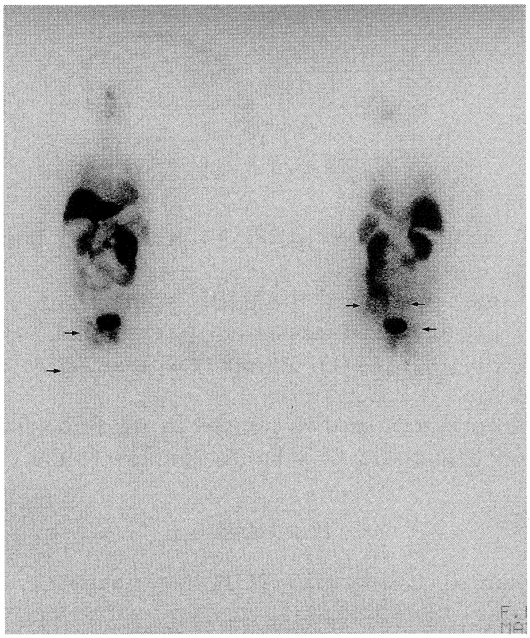

Fig 5. ^{99m}Tc-MIBI scintigraphy (left : anterior view, right : posterior view) after ^{131}I-Na treatment in Case No. 2. Increased accumulations of bone metastatic lesions in the right pubic bone, sacrum, right ischium and right femur disappeared, and those in the left sacroiliac joint and lumbar vertebra decreased.

TABLE 2. Summary of scintigraphy before and after ^{131}I-Na treatment in three patients with bone metastases from differentiated thyroid cancer

Case No	Metastatic Site(s)	^{99m}Tc-MIBI	
		Pre-Tx	Post-Tx
1	Lt. orbit	increased	decreased
	Sternum	increased	decreased
	Lt. 7th Rib	increased	decreased
	Th12	increased	disappeared
	Lt. Ilium	increased	disappeared
2	Rt. Pubic Bone	increased	disappeared
	Rt. Ischium	increased	disappeared
	Sacrum	increased	disappeared
	Rt. Femur	increased	disappeared
	L2	increased	decreased
	Lt. Sacroiliac Joint	increased	decreased
3	L3	increased	decreased
	L4	increased	decreased
	Sacrum	increased	unchanged

TABLE 3. Changes in the serum thyroglobulin (Tg) concentrations before and after ^{131}I-Na treatment

Case No	Tg(μg/L)*	
	Pre-Tx	Post-Tx
1	13,500	885
2	102,000	402
3	8,100	1,090

*Normal range (<50 μg/L)

MIBI scintigraphy accumulations in all 14 lesions of bone metastases had increased (Table 1, Figs 2, 3).

After ^{131}I-Na therapy, on ^{99m}Tc-MIBI scintigraphy, all the increased accumulations in the lesions disappeared (six lesions, 43%) or decreased (seven lesions, 50%) (Figs 4, 5), except for one lesion in the sacrum in Case No. 3 (Table 2).

Serum Tg concentrations also decreased in all three patients after ^{131}I-Na treatment compared with those of prior to therapy (Table 3).

DISCUSSION

Although computed tomography (CT) and magnetic resonance imaging (MRI) can evaluate morphological changes with high resolution, bone scintigraphy can obtain functioning information of bone metabolism, especially bone formation. Modalities such as bone scintigraphy using ^{99m}Tc-phosphorous compound, CT and MRI are used for the detection of bone metastases associated with malignant tumors.[1]

In regard to survey of the entire skeleton, bone scintigraphy is an easy method to use, whereas CT is characterized by high radiation and MRI is time-consuming. The mechanism of the accumulation of ^{99m}Tc labelled compounds in the bone is suggested to be as follows; accumulation increases when the hydroxyapatite crystal surface, bone formation, or blood flow to the bone has increased. Most bone metastatic lesions show acceleration of both bone resorption and bone formation, indicating normal bone remodeling, and an increase in accumulation.

However, when only minimal bone formation occurs in bone metastatic lesions from malignant tumors such as differentiated thyroid cancer and multiple myeloma, little accumulation is usually evident on bone scintigraphy, even though tumor cells are present. ^{99m}Tc-MIBI scintigraphy has been reported to be useful for the detection of differentiated thyroid cancer and its metastasis. However, ^{99m}Tc-MIBI normally distributes in the liver, thyroid gland, colon, and kidney. Therefore, it is sometimes difficult to detect bone metastatic lesions, because of the overlapping with organs which show normal biodistribution. Bone scintigraphy reflects a local reaction of bone metabolism, bone formation, in the bone, but does not indicate specific accumulation in neoplastic cells. The combination of both bone and ^{99m}Tc-MIBI scintigraphies will yield more sensitive and specific information on bone lesions metastasizing from differentiated thyroid cancer. ^{99m}Tc-MIBI accumulates in the metastatic lesions, resulting in increased perfusion of the metastatic site, within cell mitochondria and cytoplasma through electrical potentials generated across the membrane bilayer.[4-6]

^{131}I-Na scintigraphy has been used to detect metastasis to the lymph nodes, lung, and bone from differentiated thyroid cancer after total thyroidectomy. However, with this method, in order to image the metastatic lesions, it is necessary to restrict an iodine-containing diet, and halt thyroid hormone replacement. No replacement of thyroid hormone might lead to hypothyroidism, hypersecretion of TSH, and tumor enlargement. Compared with ^{131}I-Na scintigraphy, the advantages of ^{99m}Tc-MIBI scintigraphy are better image quality, a smaller dose of radiation, and no need to discontinue thyroid hormone administration. Another merit of ^{99m}Tc-MIBI scintigraphy is that it can be completed within one hour,[7] while ^{131}I-Na scintigraphy requires one week for imaging.

^{201}Tl scintigraphy has been reported to be useful for the detection of differentiated thyroid cancer and its metastasis.[8] The mechanism of ^{201}Tl to tumor affinity seems to be related to the acceleration of potassium metabolism in a tumor.

In the present study, on ^{99m}Tc-MIBI scintigraphy, all the lesions except one were observed to change from increased accumulations to disappearance or decreased accumulations in bone metastases from differentiated thyroid cancer after ^{131}I-Na therapy. On bone scintigraphy no changes in accumulation were noted. A combination study of bone scintigraphy and tumor scintigraphy using ^{99m}Tc-MIBI was useful in the evaluation of the detection of these lesions and therapeutical change in them.

Tumor seeking agents, ^{99m}Tc-MIBI and ^{201}Tl, accumulate in bone metastatic lesions from differentiated thyroid cancer. However, ^{201}Tl scintigraphy shows a higher tumor to background ratio, compared with ^{99m}Tc-

MIBI, but ^{99m}Tc-MIBI scintigraphy is superior in image quality to ^{201}Tl scintigraphy.

In the present study, the detectability of bone metastasis by ^{99m}Tc-MIBI was evaluated before and after ^{131}I-Na treatment in three patients with thyroid cancer. On bone scintigraphy, the detection of decreased accumulation was more difficult than that of increased accumulation. ^{99m}Tc-MIBI scintigraphy showed increased accumulation in all 14 lesions, but bone scintigraphy showed increased accumulation in eight lesions (57%) and decreased accumulation in six lesions (43%). After ^{131}I-Na treatment, none of the accumulations on bone scintigraphy had changed. On the other hand, ^{99m}Tc-MIBI scintigraphy showed disappearance (six lesions, 43%) or decreased accumulation (seven lesions, 50%) in bone metastatic lesions. ^{131}I-Na treatment was effective on bone metastasis in all three cases. On ^{99m}Tc-MIBI scintigraphy, therapeutical improvement was observed, while serum Tg level decreased. Therefore the serum Tg level was found to be a very useful tumour marker for the follow-up of patients with differentiated thyroid cancer.[7)]

In addition ^{99m}Tc-MIBI scintigraphy can be used as a diagnostic imaging modality in the follow-up of patients with differentiated thyroid cancer with elevated serum Tg levels but negative ^{131}I-scintigraphy.[9)]

^{99m}Tc-MIBI scintigraphy was useful to not only detect bone metastasis from differentiated thyroid cancer but also to evaluate changes after ^{131}I-Na treatment.

REFERENCES

1) Otsuka N, Fukunaga M, Morita K, Ono S, Nagai K, Katagiri M, Harada T : Detection of bone metastasis from thyroid cancer by bone and ^{201}Tl scintigraphy. Endocrine Surg **7** : 411-416, 1990
2) Aktolun C, Bayhan H, Kir M : Clinical experience with Tc-99m-MIBI imaging in patients with malignant tumors. Preliminary results and comparison with Tl-201. Clin Nucl Med **17** : 171-176, 1992
3) O'Driscoll CM, Baker F, Casey MJ, Duffy GJ : Localization of recurrent medullary thyroid carcinoma with technetium-99m-methoxyisobutyl isonitrile scintigraphy : a case report. J Nucl Med **32** : 2281-2283, 1991
4) Delmon-Moingcon LI, Piwnica-Worms D, Van den Abblleele AD, Leonard Holman B, Alan Davison, Jones AG : Uptake of the cation hexakis (2-methoxyisobutyl isonitrile)-technetium-99m by human carcinoma cell lines in vitro. Cancer Res **50** : 2198-2202, 1990
5) Chiu ML, Kronauge JF, Piwnica-Worms D : Effect of mitochondrial and plasma membrane potentials on accumulation of hexakis (2-methoxyisobutyl isonitrile) technetium (I) in cultured mouse fibroblasts. J Nucl Med **31** : 1646-1653, 1990
6) Miyamoto S, Kasagi K, Misaki T, Alam MS, Konishi J : Evaluation of technetium-99m-MIBI scintigraphy in metastatic differentiated thyroid carcinoma. J Nucl Med **38** : 352-356, 1997
7) Sundram FX, Goh ASW, Ang ES : Role of technetium-99m-sestamibi in localization of thyroid cancer metastases. Ann Acad Med **22** : 557-559, 1993
8) Hisada K, Tonami N, Miyamae T, Hiraki Y, Yamazaki T, Maeda T, Nakajo M : Clinical evaluation of tumor imaging with ^{201}Tl chloride. Radiology **129** : 497-500, 1978
9) Casara D, Rubello D, Saladini G, Mazzarotto R, Sotti G, Tomasella G, Pelizzo MR : Clinical approach in patients with metastatic differentiated thyroid carcinoma and negative ^{131}I whole body scintigraphy : importance of ^{99m}Tc-MIBI scan combined with high resolution neck ultrasonography. Tumori **85** : 122-127, 1999